

# Comorbidities Associated with Obstructive Sleep Apnea: a Retrospective Study

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Int Arch Otorhinolaryngol 2016;20:145–150.

## Abstract

**Introduction** Obstructive sleep apnea (OSA) is characterized by partial or complete recurrent upper airway obstruction during sleep. OSA brings many adverse consequences, such as hypertension, obesity, diabetes mellitus, cardiac and encephalic alterations, behavioral, among others, resulting in a significant source of public health care by generating a high financial and social impact. The importance of this assessment proves to be useful, because the incidence of patients with comorbidities associated with AOS has been increasing consistently and presents significant influence in natural disease history.

**Objective** The objective of this study is to assess major comorbidities associated with obstructive sleep apnea (OSA) and prevalence in a group of patients diagnosed clinically and polysomnographically with OSA.

**Methods** This is a retrospective study of 100 charts from patients previously diagnosed with OSA in our service between October 2010 and January 2013.

**Results** We evaluated 100 patients with OSA (84 men and 16 women) with a mean age of 50.05 years (range 19–75 years). The prevalence of comorbidities were hypertension (39%), obesity (34%), depression (19%), gastroesophageal reflux disease (GERD) (18%), diabetes mellitus (15%), hypercholesterolemia (10%), asthma (4%), and no comorbidities (33%). Comorbidities occurred in 56.2% patients diagnosed with mild OSA, 67.6% with moderate OSA, and 70% of patients with severe OSA.

**Conclusion** According to the current literature data and the values obtained in our paper, we can correlate through expressive values obesity with OSA and their apnea hypopnea index (AHI) values. However, despite significant prevalence of OSA with other comorbidities, our study could not render expressive significance values able to justify their correlations.

## Keywords

- ▶ apnea
- ▶ comorbidity
- ▶ polysomnography
- ▶ sleep

## Introduction

Obstructive sleep apnea (OSA) is characterized by partial or complete recurrent upper airway obstruction during sleep, resulting in periods of apnea, oxyhemoglobin desaturation, and frequent night awakenings with excessive daytime

sleepiness as a consequence,<sup>1</sup> reducing performance at work and in social activities in many cases. According to Young, the prevalence of OSA in adults between 30 to 60 years old ranges from 2% in women up to 4% in men.<sup>2</sup> A Brazilian study revealed that the incidence of OSA is ~32.8% in the population of São Paulo.<sup>3</sup>

received  
August 11, 2015  
accepted  
December 6, 2015  
published online  
March 10, 2016

DOI <http://dx.doi.org/10.1055/s-0036-1579546>.  
ISSN 1809-9777.

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The prevalence of OSA associated with high rates of morbidity and mortality increases with age and the peak occurs at ~55 years, being more prevalent in males at a ratio of 2:1. It is more common in women in the postmenopausal period.<sup>4</sup>

OSA pathophysiology has not been fully elucidated. We know that during respiratory events there is a fall in oxygen saturation, causing activation of the baroreflex, triggering a response of the sympathetic nervous system, adrenergic discharge leading to tachycardia and hypertension peaks. This process repeats itself many times during sleep in apneic patients, leading to hypersensitivity peripheral quimioireflex. This exaggerated response even in normoxia, leads to long-term dysfunction of the baroreflex, increased adrenergic discharge, cardiovascular dysfunction, systemic inflammation, and metabolic deregulation with insulin resistance and diabetes mellitus type II.<sup>5</sup>

OSA brings many adverse consequences, such as hypertension, obesity, diabetes mellitus, cardiac and encephalic alterations, behavioral, among others, resulting in significant source of public health care by generating a high financial and social impact. These comorbidities are associated with increased mortality in patients with OSA compared with the general population of the same age group.<sup>6</sup>

The risk factors for obstructive sleep apnea are obesity, age, gender, menopause, craniofacial abnormalities, smoking, alcohol use, and family history.<sup>7</sup>

OSA is a systemic disease that causes an increase in inflammatory cytokines, tumor necrosis factor  $\alpha$  (TNF- $\alpha$ ), interleukin-6 (IL-6), increased insulin resistance, and glucose intolerance.<sup>8-10</sup>

Cardiovascular diseases are now the major cause of mortality in the world.<sup>11</sup> Several studies confirm the importance of factors such as smoking, high levels of LDL-cholesterol, low HDL-cholesterol levels, diabetes mellitus, hypertension, family history, obesity, physical inactivity, central obesity, metabolic syndrome, and alcohol intake in the genesis of atherosclerosis and their clinical complications.<sup>12-14</sup> In addition to these factors, there has been recent evidence of increased cardiovascular mortality in patients with OSA.<sup>15,16</sup> Other comorbidities also associated with OSA are: depression, asthma, and GERD.

The prevalence of GERD in OSA patients is significantly higher than the general population. Recent studies have shown that treatment with a continuous positive airway pressure (CPAP) device significantly reduces the symptoms of GERD and the exposure of acid pH in the esophagus as well as improves the number of awakenings and apnea indexes.<sup>17</sup>

This work aims to analyze the prevalence of major comorbidities associated with OSA in a selected group of patients with a clinical and polysomnography diagnosis of OSA. The importance of this assessment proves to be useful, because the incidence of patients with comorbidities associated with AOS has been increasing consistently and presents significant influence in natural disease history.

## Methods

Our study received approval from the Research Ethics Committee, registered under number 437-760. We delineated an observational retrospective cross-sectional study. We carried out the evaluation by reviewing the protocol of patients with

OSA in the Otorhinolaryngology service from October 2010 to January 2013.

The evaluation protocol included anamnesis, complete physical examination, anthropometric measurements (weight, body mass index (BMI), neck circumference (NC), waist circumference (WC), pelvic circumference (CP)), and complete otorhinolaryngological exam with Nasofibrolaryngoscopy and Polysomnography type I made in the sleep laboratory with technical assistance enabled. We considered obesity a BMI > 30.

We classified the degree of apnea according to the apnea hypopnea index (AHI in: mild ( $\geq 5$  to < 15 events / hour), moderate ( $\geq 15$  to < 30 events / hour), and severe ( $\geq 30$  events / hour).

All patients filled out questionnaires with respect to diseases of the cardiovascular, respiratory, endocrine, neurological, psychiatric, genitourinary, gastrointestinal, and metabolic systems. Comorbidity diagnosis relied solely on the response to our questionnaire, and when the answer was positive as to the patient having comorbidity, the patient described the medications in use.

Inclusion criteria were patients in the OSA ambulatory cohort, patients with complete protocols, patients aged between 18 and 80 years, and patients of both genders. Exclusion criteria were patients with tumors and / or polyps in the upper airway, patients with craniofacial deformity (craniofacial deformity may already be an isolated change factor for AHI regardless of associated comorbidities), patients with previous history of airway surgery and / or abdominal surgery.

For data analysis, we compared proportions between three independent groups and applied the Fisher-Freeman-Halton exact test. When we observed significant difference, we proceeded to multiple comparisons of proportions via permutation tests. We described categorical variables by counts and proportions. Quantitative variables with normal and asymmetric distribution were described as mean  $\pm$  standard deviation and median (interquartile range), respectively. We assessed normality by visual inspection of histograms. The R (R Foundation, Vienna, Austria) software was used for statistical data analysis. All significance probabilities presented are the bilateral type and values less than 0.05 were considered statistically significant.

## Results

We evaluated one hundred patients: 84 males and 16 females, mean age of 50.05 years, ranging from 19 to 75 years. BMI ranged from 20.7 to 50.81 with an average of 28.95. **► Table 1** shows the measured anthropometric measurements.

We divided the sample in 3 independent groups according to the AHI using a cutoff: mild apnea ( $\geq 5$  to < 15 events / hour), moderate apnea ( $\geq 15$  to < 30 events / hour), and severe apnea ( $\geq 30$  events / hour). The AHI ranged from 6.7 to 98.59 with an average of 35.19; 16 patients had mild AHI, 34 patients had moderate IAH, and 50 patients had severe AHI. After splitting the sample, we analyzed comorbidities (Obesity, Hypertension, Depression, Gastroesophageal Reflux Disease, Diabetes Mellitus, Hypercholesterolemia, and Asthma) separately in relation to AHI using Fisher-Freeman-Halton exact test to determine whether

**Table 1** Descriptive variables

| Variable | Minimum | Maximum | Average | Standard deviation |
|----------|---------|---------|---------|--------------------|
| Age      | 19      | 75      | 50.05   | ± 12.86            |
| Weight   | 51.50   | 140.00  | 89.40   | ± 17.10            |
| BMI      | 20.70   | 50.81   | 28.95   | ± 4.95             |
| NC       | 32.00   | 51.00   | 41.20   | ± 3.66             |
| AC       | 53.00   | 146.00  | 101.87  | ± 14.52            |
| PC       | 48.00   | 153.00  | 105.87  | ± 12.70            |

Abbreviations: AC, abdominal circumference; BMI, Body Mass Index; NC, neck circumference; PC, pelvic circumference.

there was significant difference in proportions between the three groups (Fisher-Freeman-Halton test,  $p = 0.010$ ). Comorbidities were associated in 56.2% patients diagnosed with mild OSA, in 67.6% with moderate OSA, and in 70% of patients with severe OSA. The prevalence in relation to associated comorbidities were: obesity (32%), 30 men and 2 women, among them, 23 had severe OSA, 7 moderate OSA and 2 mild OSA, hypertension (39%), 38 men and 1 woman, among them, 23 had severe OSA, 12 moderate OSA and 4 mild OSA; depression (19%), 16 men and 3 women, among them, 7 had severe OSA, 7 moderate OSA and 5 mild OSA; gastroesophageal reflux disease (18%), 10 patients had severe OSA, 7 moderate OSA and 1 mild OSA; diabetes mellitus (15%), among them, 9 had severe OSA, 5 moderate OSA, and 1 mild OSA 1; hypercholesterolemia (10%), 6 of them had severe OSA and 4 moderate OSA; and asthma (4%) all of them had severe OSA. ► **Table 2** shows the final comparative results.

For  $p$  less than 0.05 on the Fisher-Freeman-Halton test (significant difference observed), we used the permutation test for multiple comparisons of proportions to find out

whether there was significant difference between the degrees of apnea. We only observed significant  $p$  for obesity ( $p = 0.013$ ) and, after applying multiple comparisons, there was no difference in obesity proportion between mild AHI when compared with those with moderate AHI (12.5% versus 20.6%;  $p = 0.849$ ; permutation test); the obesity rate was statistically lower in the comparison between the mild AHI group and severe AHI group (12.5% versus 46.0%;  $p = 0.035$ ; permutation test), and between moderate AHI group when compared with severe AHI group (20.6% versus 46.0%;  $p = 0.040$ ; permutation test). ► **Table 3** shows the results of multiple comparisons for obesity proportion.

## Discussion

The importance of OSA and its associated comorbidities in otorhinolaryngology has increased considerably in recent years. Present among the main complaints in specialty clinics, this disease causes chronic inflammation and decrease in quality of life.

The prevalence of OSA is strongly associated to overweight and obesity in cross-sectional and clinical studies.<sup>18-24</sup> Obesity is known to be a cause of AOS and is likely to be a consequence thereof. This complexity makes it especially

**Table 3** Multiple Comparisons - Obesity in relation to the apnea hypopnea index

| Variable | Comparison between AHI index                          | P-Value |
|----------|---|---------|
| Obesity  | $5 \leq \text{AIH} < 15$ vs $15 \leq \text{AIH} < 30$ | 0.849   |
| Obesity  | $5 \leq \text{AIH} < 15$ vs $\text{AIH} \geq 30$      | 0.035   |
| Obesity  | $15 \leq \text{AIH} < 30$ vs $\text{AIH} \geq 30$     | 0.040   |

Abbreviations: AHI, apnea-hypopnea index.

**Table 2** Prevalence of comorbidities x OSA severity

| Variable             |     | Mild OSA<br>N = 16 | Moderate OSA<br>N = 34 | Severe OSA<br>N = 50 | Total<br>N = 100 | P-Value            |
|----------------------|-----|--------------------|------------------------|----------------------|------------------|--------------------|
| Obesity              | Yes | 2(12.5%)           | 7(20.6%)               | 23(46.0%)            | 32(32.0%)        | 0.010 <sup>3</sup> |
|                      | No  | 14(87.5%)          | 27(79.4%)              | 27(54.0%)            | 68(68.0%)        |                    |
| Hypertension         | Yes | 4(25.0%)           | 12(35.3%)              | 23(46.0%)            | 39(39.0%)        | 0.291 <sup>3</sup> |
|                      | No  | 12(75.0%)          | 22(64.7%)              | 27(54.0%)            | 61(61.0%)        |                    |
| Depression           | Yes | 5(31.3%)           | 7(20.6%)               | 7(14.0%)             | 19(19.0%)        | 0.273 <sup>3</sup> |
|                      | No  | 11(68.8%)          | 27(79.4%)              | 43(86.0%)            | 81(81%)          |                    |
| GERD                 | Yes | 1(6.3%)            | 7(20.6%)               | 10(20.0%)            | 18(18.0%)        | 0.467 <sup>3</sup> |
|                      | No  | 15(93.8%)          | 27(79.4%)              | 40(80.0%)            | 82(82.0%)        |                    |
| DM                   | Yes | 1(6.3%)            | 5(14.7%)               | 9(18.0%)             | 15(15.0%)        | 0.601 <sup>3</sup> |
|                      | No  | 15(93.8%)          | 29(85.3%)              | 41(82.0%)            | 85(85.0%)        |                    |
| Hypercholesterolemia | Yes | 0(0.0%)            | 4(11.8%)               | 6(12.0%)             | 10(10.0%)        | 0.442 <sup>3</sup> |
|                      | No  | 16(100.0%)         | 30(88.2%)              | 44(88.0%)            | 90(90.0%)        |                    |
| Asthma               | Yes | 0(0.0%)            | 0(0.0%)                | 4(8.0%)              | 4(4.0%)          | 0.214 <sup>3</sup> |
|                      | No  | 16(100.0%)         | 34(100.0%)             | 46(92.0%)            | 96(96.0%)        |                    |

Abbreviations: DM, Diabetes Mellitus; GERD, Gastroesophageal Reflux Disease; N, number of individuals.

difficult to interpret the relationship between the two conditions and between OSA and its relation to cardiovascular disease and metabolic disorders.<sup>18,19,25-28</sup> In a random sample of middle-aged patients, taken from a cohort study of Wisconsin, 1-point increase in the standard deviation obesity was associated with an increase of 4 times the risk of sleep apnea.<sup>20</sup>

According to a survey conducted by the Brazilian Ministry of Health in 2012, with retrospective of six years, the obese percentage increased from 11.6% to 17.4%.<sup>29</sup> In the current study, the prevalence of obesity in OSA patients was 32%, almost double that of the general population. Moreover, it was the only comorbidity which obtained significant value ( $p < 0.05$ ) confirming the direct relationship of its prevalence to OSA and correlating directly with the severity.

Previous clinical studies indicate that OSA may be associated with hypertension and ~50% of patients end up having the two associated pathologies.<sup>30-32</sup> Several cross-sectional studies suggest an independent association between OSA and hypertension.<sup>33,34</sup> Discrepant findings were observed in the Sleep Heart Health Study, a prospective cohort study to monitoring of cardiovascular outcome in patients diagnosed with sleep disorders. The  $p$  value for hypertension was significant with the increase of the AHI, however, this relationship was attenuated and was not significant after a correlation with BMI, suggesting that much of the relationship between AHI and hypertension resulted from obesity.<sup>35</sup>

In relation to arterial hypertension, the most recent data in Brazil, from 2012, showed that average prevalence of hypertension in the Brazilian population was 24.3%.<sup>29</sup> In our study, 39% of patients had hypertension, a higher rate than the general population and a higher rate than the overall percentage to obese patients, however there was no significant correlation value between OSA and hypertension. One explanation for these results is that the highest difference between the proportions of hypertension variable was 25.0% (mild AHI) versus 46.0% (severe AHI); a difference of 21% is not enough to observe a statistically significant difference, whereas the obesity variable produced a difference of 25.4%, enough to produce a statistically significant difference. In a study where one of the groups have a significantly reduced  $N$  (mild AHI,  $N = 16$ ), the differences between the values must be greater to observe statistical significance.

Psychiatric symptoms or associated disorders with OSA include depression, anxiety, post-traumatic stress disorder, among others.<sup>36-39</sup> They seem to be more common and more severe in females with OSA than in males.<sup>38</sup> Symptoms of depression, though prevalent in OSA do not correlate with severity.<sup>38,40,41</sup> In our study, we found 19% of patients with depressive symptoms using medication, with no significant differences between the AHI values.

Several authors have evaluated the possible association between GERD and OSA.<sup>42-47</sup> However, only a single study confirmed the direct relationship between the two diseases.<sup>47</sup> In our study, 18% of OSA patients were diagnosed with GERD, with no correlation to the severity of the apnea.

The association between OSA and type II DM is recognized.<sup>48,49</sup> Cross-sectional studies suggest that up to 30% of

patients with OSA have type II DM and up to 86% of obese patients with type II DM have OSA.<sup>24,50-52</sup> However, due to the presence of variables, especially obesity, research has not demonstrated a direct causal relationship between OSA and alterations in glucose metabolism.<sup>53,54</sup> Fifteen per cent of our patients had DM associated with OSA, lacking evidence of correlation between AHI and DM type II.

Data from Sleep Heart Health Study indicated that total cholesterol levels were associated with AHI values, after correlation with age and BMI.<sup>23</sup> Most of the other clinical studies that discuss the relationship between OSA and dyslipidemia have a reduced number of participants; however, when comparing studies of dyslipidemia values with individuals without OSA, these studies have shown an increase in lipid abnormalities in patients with OSA.<sup>55-57</sup> The AHI was the main determinant for cholesterol dysfunction. These observations suggest that cholesterol tends to be altered in patients with OSA and partly contributes to increase the cardiovascular risk.<sup>58</sup> In our study, 10% of all patients had hypercholesterolemia and all of them had moderate or severe AHI, suggesting a correlation between AHI and hypercholesterolemia, although no statistical significance value was found.

Several publications have discussed the relationship between asthma and OSA.<sup>59-63</sup> Salles et al reported that OSA is prevalent in patients with asthma and is associated with disease severity. Asthma is associated with acute and chronic inflammation that affects the respiratory muscles, including upper airway dilators.<sup>64</sup> The biological mechanism that correlates asthma to OSA would be the fact that the inflammation of the upper airways caused by asthma would facilitate the collapse of the muscles favoring OSA. National Asthma Education and Prevention Program recommends screening of OSA in patients with asthma because treatment of OSA has proven to be effective in improving symptoms of asthma.<sup>65,66</sup> In our study, only 4% of patients had asthma associated with OSA, although it has not presented expressive values; only patients with severe apnea had associated asthma.

There are limitations to this study. The first is due to a modest sample of patients ( $n = 100$ ), second, we did not rely on a control group without OSA and correlate with associated comorbidities.

We identified a statistically significant relationship between OSA and obesity, noting that obesity is more prevalent the higher the AHI. In relation to other comorbidities, we could not obtain statistical significance values, however a higher percentage of patients with associated comorbidities have a high AHI. Based on data obtained in our work and from the current literature, we can correlate some aspects between OSA and associated comorbidities, however, further research on this topic may be able to reveal more obvious correlations between the pathologies.

## Conclusion

The causal relationship of the OAS with the associated comorbidities has gained notoriety in the literature with the emergence of prospective studies using polysomnography in large



numbers of patients. Current data supports OSA as an independent risk factor for the emergence of comorbidities. Patients with risk factors for sleep apnea should be properly investigated, since the failure to identify the sleep disorder may contribute to therapeutic failure in the treatment of comorbidities. Based on the current literature data and the values found in our work, we can correlate with significance obesity values with OSA and their AHI values; however, despite significant prevalence of OSA with other comorbidities, we cannot rely on significant values in our study to justify their correlations. Research with control group and a higher number of cases are necessary for further investigations and correlations.

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